COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

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For the award of the degree of

M.CH (UROLOGY) –BRANCH -IV

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DECLARATION

I solemnly declare that this dissertation entitled, **"COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE"** is a bonafide work done by me in Department of Urology, Madras Medical College and Government General Hospital, under the guidance and supervision of the Professor **R.Jeyaraman, M.S, M.Ch(Uro).,** Professor and Head of Department, Department of Urology, Rajiv Gandhi Government General Hospital, Chennai. This dissertation is submitted to The Tamil Nadu Dr. M.G.R Medical University, in partial fulfillment of requirement for the award of Degree of **M.Ch Urology.**

Place: DR.J.INDUJA

Date:

CERTIFICATE

This is to certify that the dissertation titled **"COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE"** submitted by DR.J.INDUJA appearing for M.Ch(Urology) degree examination in August 2014 is a bonafide work done by her under my guidance and supervision in fulfillment of requirement of the Tamil Nadu Dr. M.G.R. Medical University. I forward this to The Tamil Nadu Dr. M.G.R. Medical University, Chennai.

The Dean
Madras Medical College,
Rajiv Gandhi Government
General Hospital,
Chennai – 600 003

PROF.R.Jeyaraman, M.S.,M.Ch,
Professor & Head of the Department,
Department of Urology,
Madras Medical College
Chennai -600 003.

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INTRODUCTION

One of the most common cancers diagnosed in men is carcinoma prostate. Because of improvements in diagnostic testing, its incidence has been increasing. In patients with carcinoma prostate, ultra sonogram guided biopsy has been the investigation of choice in men with increased serum prostate specific antigen or a nodular prostate. Targeted biopsies will be helpful in increasing the sensitivity of systematic biopsy.

Micro-bubble contrast agents are used as innovative technology to enhance detection of prostate cancer. Several studies have demonstrated that contrast enhanced ultrasound (CEUS) of prostatic blood flow helps in visualization of cancerous lesion and to target biopsy. Biopsy from target lesion helps in detecting more cancers with lesser cores .CEUS has been shown to detect cancers with higher Gleason scores, which improves cancer grading.

Micro bubble contrast agent images the microvasculature in the prostate, especially in carcinoma, these contrast agents increase the sensitivity in detecting carcinomatous lesions.

We undertook this study to find the efficacy of CE sonography for detection of prostate in patients with PSA >4 ng/ml and compare this with conventional system.

AIM AND OBJECTIVE

Primary objective: To assess the efficacy of contrast enhanced color Doppler ultrasound guided biopsy to detect prostate cancer.

Secondary Objective: To compare prostate cancer detection with contrast enhanced ultrasound compared and conventional systematic biopsy and the impact on Gleason score.

REVIEW OF LITERATURE

CARCINOMA PROSTATE

Epidemiology

In men, carcinoma prostate is the most common malignancy with increasing an incidence over the past decade. The average age of diagnosis is 70 years and it occurs in 95% men between ages of 45-89 yrs. There is an exponential increase in incidence and mortality from prostate cancer after the age of fifty. Prostate cancer accounts for 2% of cancers in men younger than 50.There is 16.72% risk of disease in one's lifetime and 2.57 % risk of death. A positive family history of prostate cancer increases the chance of the disease at an age younger than the persons without family history. Metastatic, incurable disease occurs in 50% of men with carcinoma prostate. To improve patient survival and to advocate a definitive treatment, early diagnosis of localized tumor is essential.

RELEVANT ANATOMY:

Prostate gland lies adjacent to bladder neck proximally and distally it is continuous with the membranous urethra. The adult gland weighs 18 to 20g. The gland measures about 3 cm in length, 4 cm in width and 2 cm in depth. The prostatic part of urethra traverses the gland closer to its anterior surface. The ejaculatory ducts

enter the base on its posterior aspect and run in an oblique fashion, terminating adjacent to the verumontanum.

The prostate has an anterior, posterior and lateral surface with an apex inferiorly and base superiorly. The prostate is composed of 70% glandular elements and 30% fibromuscular stroma. McNeal separated the glandular prostate into four distinct regions.

Central zone (CZ)

It comprises about 25% of gland. The ducts of this region open around ejaculatory duct. This zone is responsible for 1-5% of adenocarcinoma.

Peripheral zone (PZ)

This zone occupies the Postero-lateral aspect and forms bulk of the gland (70%).The ducts of this zone drain into prostatic sinus. It is responsible for

Origin of up to 70% of prostate adenocarcinoma.

Transitional zone (TZ)

This zone accounts for 5-10% of prostatic glandular tissue.20% of prostate cancer arise from TZ. This is the commonest zone for BPH.

Anterior fibromuscularstroma (AFS)

This is the nonglandular portion and it is rarely invaded by carcinoma.

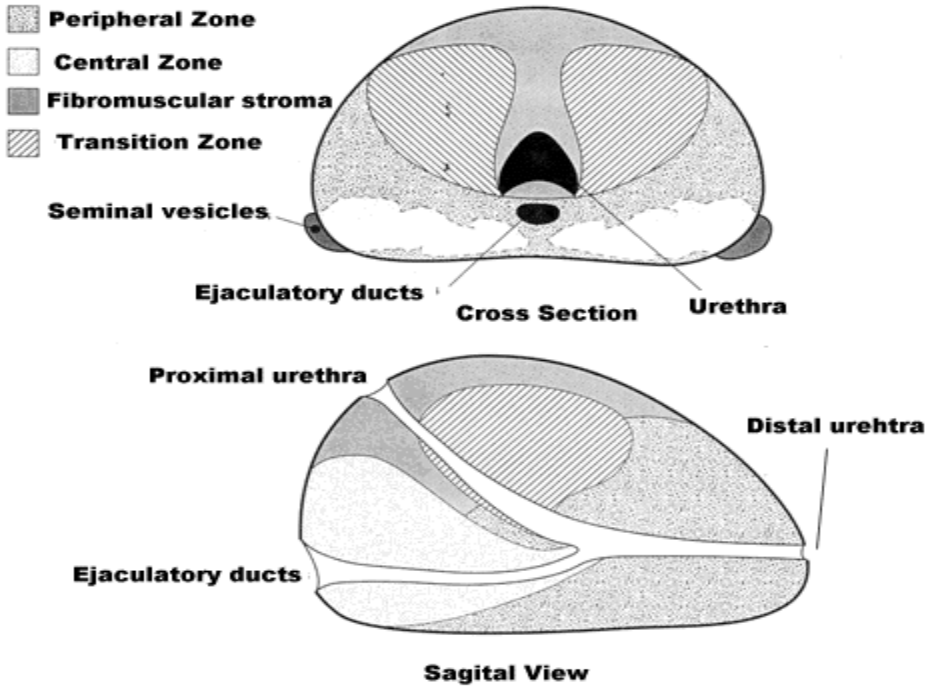


Fig 1 Zonal Anatomy of Prostate

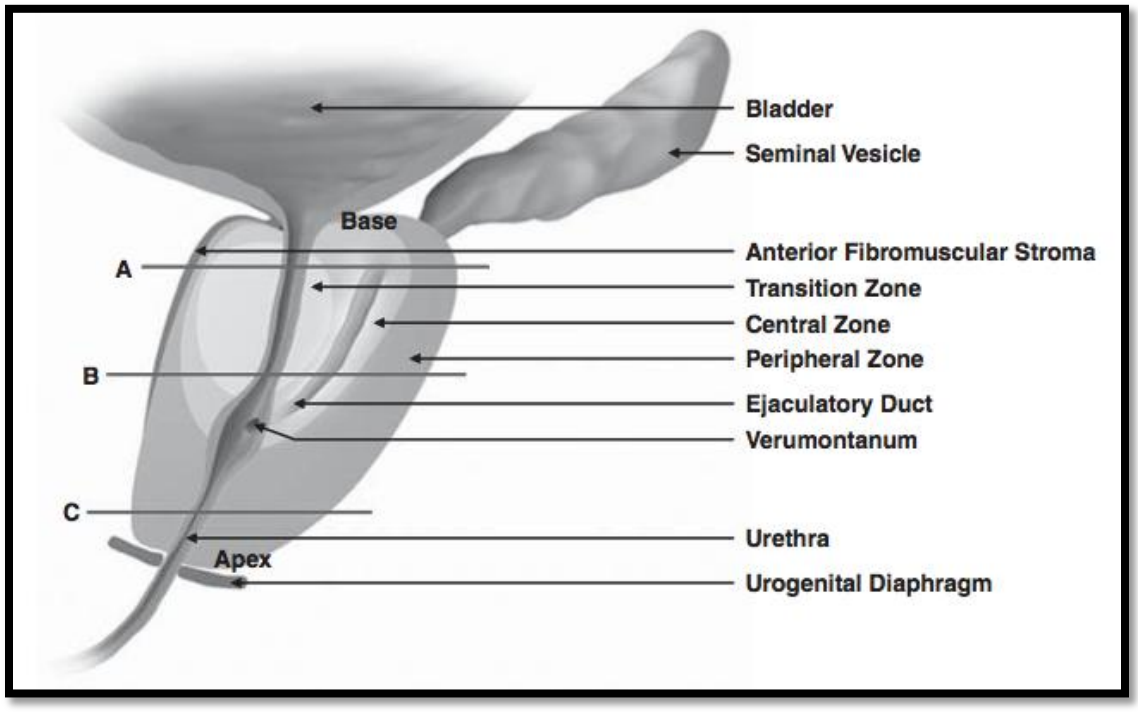


Fig 2 Diagrammatic representation of the prostate gland-Sagittal view.

ETIOLOGY:

Genetics

Several variants in the chromosome 8 (8q24 region) ; Gene alterations on chromosome 1,X,17*; BRCA-2*mutations; germline mutations in *HOXB13* ; *PCAP* gene; *HPC1*genearethe risk factors for prostate cancer.

5-10 % cases may have familial predisposition .The risk of developing prostate cancer, increases with family history and they present about 6-7 years earlier.

Diet

Fat intake and obesity increases the risk.

Hormones

Androgens influence the development, maturation, and maintenance of the prostate, affecting both proliferation and differentiation of the luminal epithelium. Androgen exposure of the prostate plays an important role in prostate carcinogenesis. Eunuchs do not develop prostate adenocarcinoma, which is indirect evidence. Also, androgen ablation is one of the treatment option of prostate carcinoma.

5-alpha reductase

Studies shows an increased occurrence of prostate tumors of high-grade, in patients on finasteride or dutasteride compared with placebo.

PATHOLOGY:

Most (95%) are adenocarcinomas.

About 4% are transitional cell carcinomas

Fewer than 1% are squamous cell carcinomas. In many cases, squamous cell prostate carcinomas arise after hormone or radiation treatment.

Neuroendocrine carcinomas (Rare)

Synchronous occurrence of the multiple zones of the prostate gland commonly occurs and so most of them are multifocal.

CLINICAL FEATURES:

At present, most of the prostate cancers are seen in asymptomatic patients. Diagnosis in those cases is done based on screening of PSA levels or digital rectal examination findings.

Signs and symptoms:

Symptoms of prostate cancer include:

- Hematuria
- Urinary complaints or retention
- Back pain

Physical examination alone could not accurately differentiate BPH from cancer.

In advance diseased patients, findings may include:

- Bony tenderness
- Cancer cachexia
- Adenopathy
- Lower-extremity lymphedema
- Bladder over distension

Local spread and metastasis:

Prostate carcinomas are locally invasive. The peripheral-zone cancers extend into the seminal vesicles and ejaculatory ducts.

The route of distant metastasis is not clear. The seed-and-soil theory, states that, “tissue factors may allow for preferential growth in some tissues, like bone”. The mechanical theory states that, “By direct spread through the venous spaces and

lymphatics , cancer can spread to the lumbar spine ”. Prostatic capsule penetration and extension along the vascular or perineural spaces occurs at a later stage.The transitional-zone cancers spread to the bladder neck.

Adrenal, liver, Lung metastases may occur.The bone metastasis can occur early, commonly without significant lymphadenopathy.

The doubling time is longer than 4 years, in most cases. Only a few percentage of prostate carcinomas, double in less than 2 years.

DIAGNOSTIC MODALITIES :

Digital rectal examination (DRE)

Prostate-specific antigen (PSA) measurement

Transrectal ultrasound (TRUS)-guided prostate biopsy.

Digital rectal examination:

Early detection of prostate cancer was based mainly on DRE before PSA era. DRE missed a substantial proportion of early cancer due to observer variability.There is an increased risk of prostate cancer in patients with abnormal DRE and so serum PSA and DRE are used together for prostate cancer detection.

Screening:

The American Cancer Society (ACS) recommends that, after discussion with themedical personnel about the risks, uncertainties, and benefits of screening, men must decide the option of screening for prostate cancer.

The recommended age for screening is:

- At an early age , with several first-degree relatives with prostate carcinoma- 40 years of age
- Before 65 years of age with a first-degree relative with prostate cancer and for African Americans - 40 or 45 years of age
- With at least a 10-year life expectancy and at average risk - 50 years of age

The USPSTF (US Preventive Services Task Force) is against any routine PSA-based screening for prostate tumors. This recommendation, is however considered controversial.

Prostate Cancer Screening:

The two main components used in prostate cancer screeningare DRE and PSA evaluation .Transrectal ultrasonography (TRUS) has established a major role in directing prostatic biopsies , but it may have a high false positive rates.

Prostate-Specific Antigen:

When PSA testing was first used, the upper limit of normal was thought to be 4ng/mL. However, subsequent studies indicate that there is no absolute PSA level that guarantees the absence of prostate cancer. The risk of this disease increases, as the PSA level increases.

When the level is 1 ng/mL, cancer is seen in about 8% of men. When the PSA level is about 4-10 ng/mL, prostate cancer is detected in about 25%; with a level > 10 ng/mL, the chance is much higher.

A cutoff value of PSA of 3 ng/mL or higher as an indication for sextant biopsy,is placed by ERSPC (European Randomized Study of Screening for Prostate Cancer) .

Shao et al suggested that in the absence of any method to distinguish aggressive from indolent cancers, lowering the PSA cutoff might increase the chance of overdiagnosis and overtreatment.

Many approaches have been made to improve the accuracy of PSA to detect the prostate cancer. These include PSA velocity level and the free PSA percentage.

Factors Influencing PSA:

- Age
- Race
- Prostate volume.
- Androgens
- Metabolic factors -Obesity
- Presence of prostatic disease

Any architectural disruption in normal prostate allows PSA to gain access into circulation leading to elevations of serum PSA. Elevated PSA occurs in diseases like BPH, prostatitis, prostate cancer and prostatic manipulation. Prostate directed treatments decrease the volume of prostatic epithelium available for PSA production and decreases the amount of PSA produced per cell. Both type 1 and type 2 5α-Reductase inhibitors used for BPH treatment lowers PSA levels.

Clinical use of PSA:

The serum PSA level indicates measurement of both free PSA and complexed PSA. (ACT) .The detection of organ confined prostate cancers is increased by the use of PSA. The prostate cancer detection on biopsy increases directly with PSA level. Detection rate of prostate cancer and detectionof cancers with a more favorable prognosisis increased by combined PSA and DRE.

PSA velocity:

To calculate velocity, at least 3 consecutive measurements over a period of, at least 18-24 months should be used. Guidelines from the National Comprehensive Cancer Network recommend that PSA velocity be considered in the context of the PSA level.

The PSA velocities that is suspicious for cancer:

- PSA velocity of 0.75 ng/mL/y, when the PSA is 4–10 ng/mL.
- PSA velocity of 0.35 ng/mL/y, when the PSA is ≤2.5 ng/ml.

Vickers et al in 2011 questioned the PSA velocity concept. In his study, PSA velocity levels, with a comparable specificity to PSA level levels, showed a lower sensitivity, particularly for high-grade cancers and clinically significant prostatic tumors. He concluded that, "PSA velocity would add little to the predictive accuracy of positive DRE or high PSA levels and would significantly increase the number of men recommended for prostatic biopsy". This controversy has not been resolved.

Bound versus free PSA:

The measurement of bound and free PSA can help to differentiate cancer from benign prostatic hyperplasia. Free PSA is calculated as a % of total PSA.

A recommendation for or against prostatic biopsy in men with a PSA level of 4-10 ng/mL can be done based upon free PSA percentage. When the free PSA percentage is lower, then there is a higher likelihood of cancer.

Typically, a free PSA > 25% is taken as normal. Some investigators recommend prostatic biopsy when the free PSA is < 18%; other expertsadvise a cutoff value of 12%. Many investigators however recommendsthat prostatic biopsy, in men with a PSA level of 4-10 ng/ml, can be done without any additional free-PSA test.

Transrectal ultrasound (TRUS)-guided prostate biopsy

TRUS and PROSTATE

NORMAL SONOGRAPHIC APPEARANCE:

Images are shown as if one stands at the feet of a supine patient and looks headward. The rectum is displayed at the bottom of the screen, with the ultrasound beam arising from within the rectum. In transverse section, left side of the patient is seen on the image right side, with anterior abdominal wall on the top of the screen. In sagittal section, on the image left side, the head side of the body is located.

Axial Ultrasound Anatomy:

The seminal vesicles are seen as bilateral hypoechoic, multiseptated structures at the level superior to the base of the prostate gland. The vas deferens is situated posterior to the seminal vesicles and they enter the prostate at midbase, where they join to form the ejaculatory ducts. The two ejaculatory ducts finally open into the verumontanum. The peripheral zone is uniformly homogeneous and is slightly more echogenic than the transition zone. The peripheral zone echogenicity is commonly taken as the standard for echogenicity in the prostate gland and is said to be isoechoic.The margin of the prostate gland is sharp except in the region posterolaterally where the neuro vascular bundles enters the gland making the margin blurred.

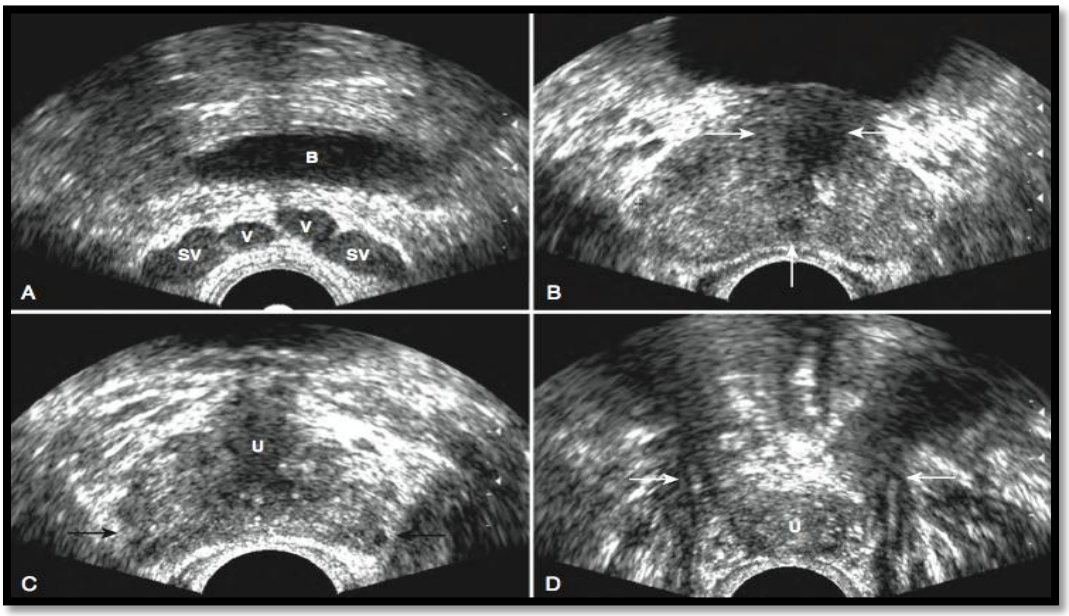


Fig 3**Axial Sonographic Examinations of The Prostate Gland**

A, Axial image above base showing the seminal vesicles (SV) and vas deferen(V); B, bladder.B**,** Axial scan at the mid glandular level. The normal hypoechoic muscular internal urethral sphincter is shown as horizontal arrowsand the ejaculatory ducts (vertical arrows). **C,** Axial scan at the lower third of prostate shows urethra (U) as hypoechoeic region. Most of the visible gland at this level is peripheral zone. The posterolateral aspects (arrows) have an irregular outline, due to the entrance of the neurovascular bundles. **D,** Axial scan just below apex of prostate showing the cross section of distal urethra (U).Pelvic sling muscles are visible (arrows).

Sagittal Ultrasound Anatomy:

On midsagittal view, the hypoechoeic muscular internal urethral sphincter can be seen extending from the bladder to verumontanum. The anterior fibromuscular zone forms an ill defined area anterior to the internal sphincter. At the verumontanum, the distal urethra angulates slightly anteriorly and finally exits the apex of the gland. In the mid plane the ejaculatory ducts are seen as hypoechoic tracts running from the vas deferens to the centrally located verumontanum. Para-sagittally, the anterior transition zone can be seen separated from the posteriorly lying peripheral zone by the surgical capsule. The seminal vesicles and vas deferens are seen above the base.

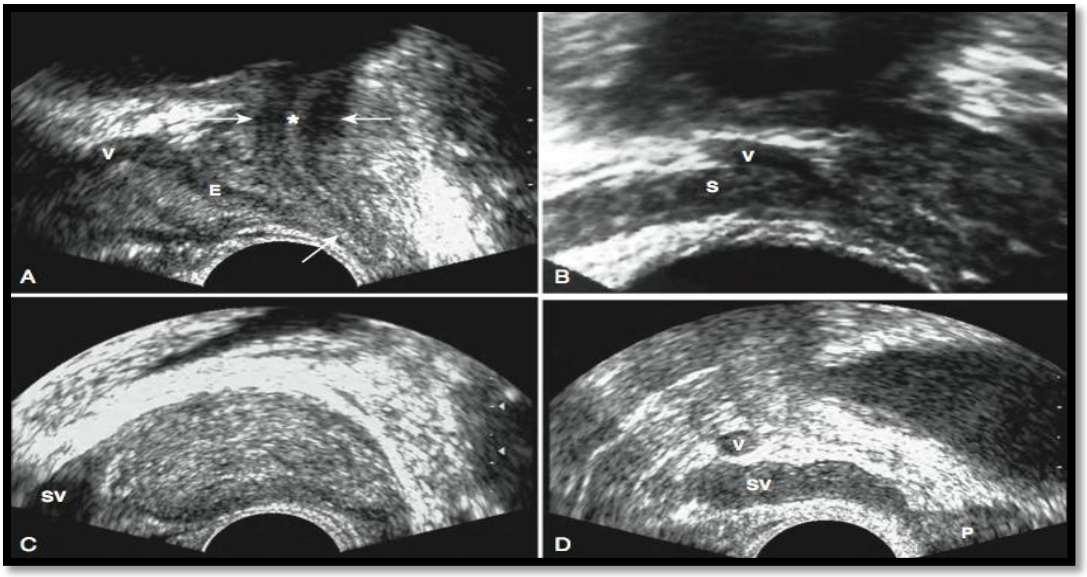


Fig 4 Sagittal Sonographic View Of Prostate Gland

A, Mid sagittal view showing the internal urethral sphincter (white arrows), with the echogenic collapsed urethra (*). The ejaculatory ducts (E) runs from the vas deferens (V) to the verumontanum (oblique arrow). **B,** Mid sagittal view at base showing the vas deferens (V) and adjacent seminal vesicles (S) as they are entering the prostate gland.**C,** Parasagittal view showing the lateral prostate, as homogeneous and isoechoic structure occupying almost totally of peripheral zone tissue; SV, seminal vesicle.**D,** Parasagittal view above the prostate showing the seminal vesicles (SV)and vas deferens(V)at the level above the prostate (P).

Method of scanning:

The patient is made to lie in a left lateral decubitus position for the scanning. Rectal cleansing by self administered enema is generally done before the scan. Laxatives may be given in patients who cannot administer the enema. It is must to do a digital rectal examination before inserting the probe to make sure no rectal abnormalities that will interfere with safe probe insertion. After lubrication, the transrectal probe is gently inserted into the rectum. To lessen the discomfort, lidocaine gel is be used as the lubricant in patients with tight sphincters or anal pathology such as hemorrhoids or fissures. End-fire probe may be inserted by direct vision to follow the curve of the rectal canal and lessen patient discomfort.

When examining the prostate gland, a systematic approach works best. First the prostate is scanned in gray scale with representative images taken, in the axial plane, from the base, to the urethral level at the apex, then secondly in the sagittal plane, from right lobe to mid plane to left lobe. Then, the scanning is done with Doppler imaging in the axial plane to allow evaluation of vascular symmetry. Measurements are then taken: axial width (W; right to left), anteroposteriorly (AP; anterior midline to rectal surface), length (L; head to foot). **Prostate volume** is measured with the formula: volume = 0.5236 *(W *AP*L)

Transrectal ultrasound is used in prostate cancer

- To Guide biopsy
- To Guide therapy
- To Measure volume

Indications for Prostate Biopsy :

1.Abnormal DRE.

2.PSA of 10 ng / mL or greater. Some studies reduced the PSA criterion to 4 or sometimes even 2.5 ng / mL.

3.Nodule seen at TRUS.

4.High PSA velocity.

5.Positive chips at TURP.

6.Males with metastatic adenocarcinoma, with undetermined primary.

Contraindications to Prostate Biopsy

- Significant coagulopathy
- Painful anorectal conditions
- Severe immunosuppression
- Acute prostatitis

Preparation:

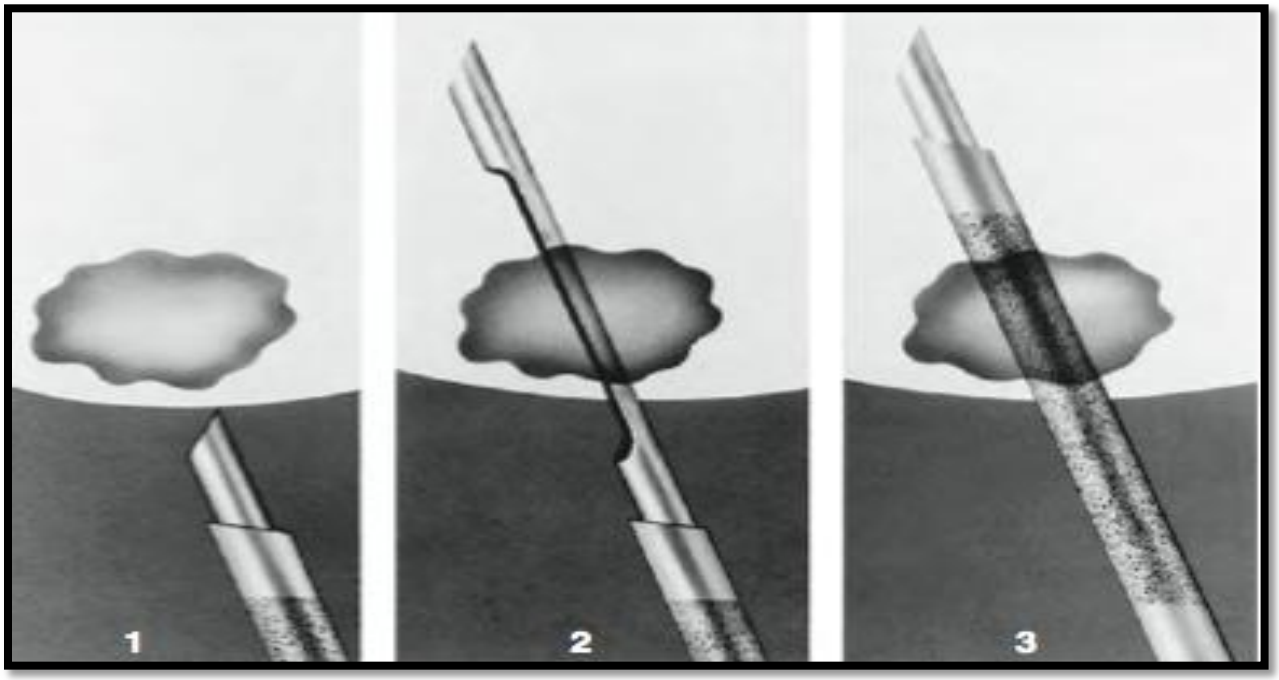
At the same visit, it is required to prepare for both TRUS and biopsy .If benign cause is found on TRUS, biopsy can be avoided.

Informed consent must be done. A broad-spectrum antibiotic like quinolones (ciprofloxacin) is given, one dose an hour before and after the biopsy for several days. In patients who are using anticoagulation agents biopsy should not be done , until these drugs have been stopped for several days, depending on the drugs. Aspirin-induced coagulation abnormalities are not severe enough to avoid safe biopsy. Biopsy is not to be done during urinary infections. It is necessary to wait 4 to 6 weeks for symptoms to subside and to confirm antibiotic sensitivities to appropriate prophylaxis for biopsy. Before doing prostate biopsy, endocarditis prophylaxis for genitourinary procedures is no longer required, in patients with valvular heart disease.

Technique:

The patient is made to lie in the decubitus position. A DRE is done before inserting the probe to palpate the prostate and to make sure that probe insertion will be safe. Insert the probe with needle guide attached at the outset to save time and examine the prostate. Local anesthesia decreases the discomfort of the biopsy. By direct injections of the anesthetic drug into the gland, anesthesia may be virtually instantaneous in most of the patients. Anesthetic gel can also be used.

The **automatic biopsy gun** with 18-gauge needles will have good patient acceptance and safety. By using the targeting line, the probe and contained needle can be moved to the target. Then, a simple, swift motion is done to advance the gun and needle tip to the surface of the lesion. Once they are in position, the device must be triggered and the needle should be advanced for approximately 2 to 3 cm. First, the inner stylet advances, and then, finally the outer sheath advances to get the tissue core and it traps it in the beveled portion of the inner needle.



Mechanism of needle function .1. Advancing the closed needle to the lesion. 2. By triggering, stylet of the inner chamber enters the lesion. 3. Finally the outer sheath enters and cuts off and acquires the sample.

First sample suspicious areas, in patients who cannot tolerate the entire procedure, and finish with systematic sampling. It is must to avoid biopsy through the ejaculatory ducts, urethra and internal urethral sphincter because it may lead to considerable urethral bleeding and major injury to those structures. After removing the probe out, the site is palpated for hematomas, and if it is present, finger pressure must be applied for approximately a minute to stop bleeding. After finishing the procedure , the patient must be kept for an hour and in that the first 20 minutes in lying down posture and the remainder seated. This prevents problems which are caused by the late onset of vasovagal complications

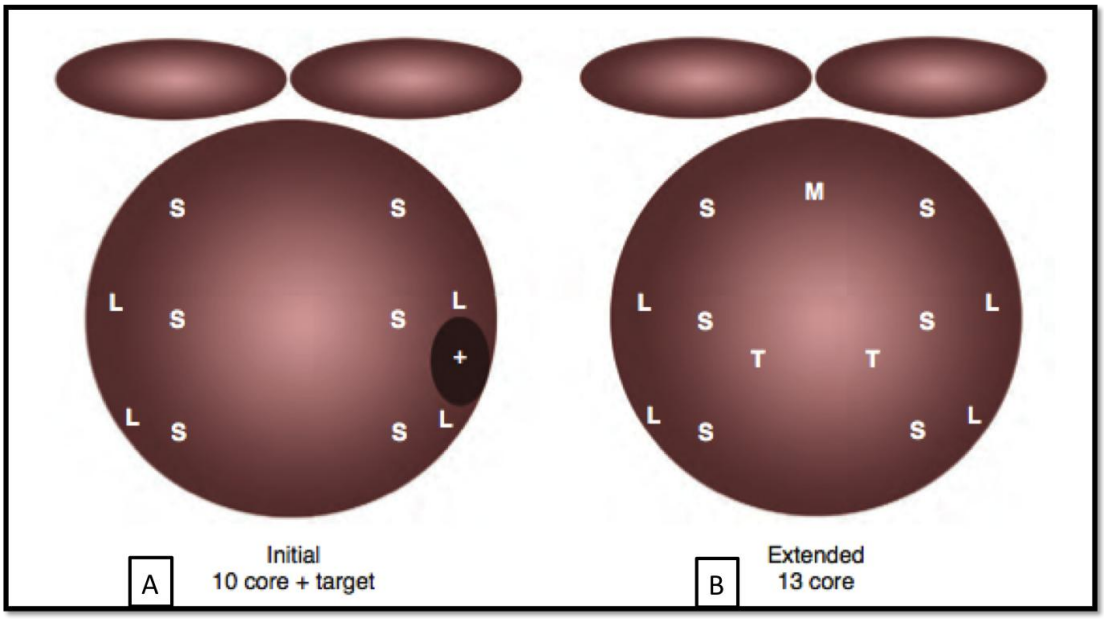


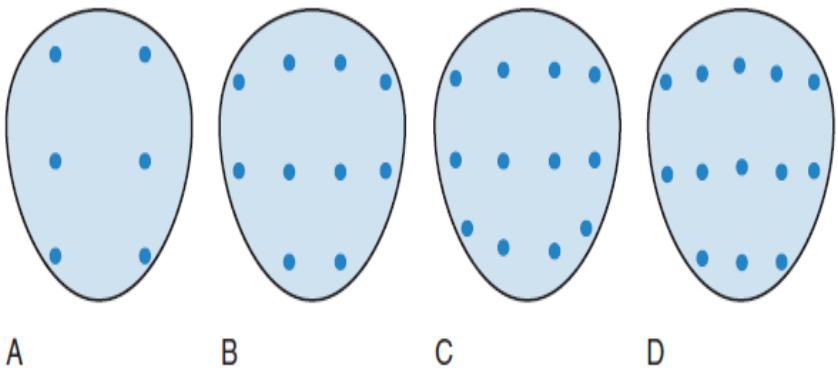
Fig 5 Biopsy Protocol

Number of samples and locations of prostate biopsy:

The number and locations are controversial. Initially only suspicious areas are thought to be sampled. It was later found that only about 50% -70 % of hypoechoic regions contained cancer, and that cancer may also be present in normal-looking areas of the prostate. Therefore "targeted + systematic" sextant (six-core) biopsy is done.

Subsequently, increased numbers of biopsy samples have been suggested as about 30% of cancers were not diagnosed by the sextant biopsy. So, ten to 12 cores are held to be appropriate on the initial visit.

So at the initial visit , suspicious hypoechoic areas are sampled first, then a systematic 10 to 12–core pattern of biopsy is done. Typically, samples are taken from the peripheral zone at the apex, middle and base of the prostate gland, both medially and laterally of each lobe.



A – sextant biopsy (Hodge et al)

B – 10 core biopsy (Presti)

C – 12 core biopsy

D – 13 core biopsy (Eskew

Side Effects and Complications:

Minor side effects like bleeding in urine, sperm, and stool may be common and is seen in most of the patients after transrectal biopsy. Major complications due to prostate biopsy that may require further intervention have been low, about 1% to 2%, which are independent of the needle size, or approach or mode of guidance. These significant complications include large hematoma, significant rectal bleeding, urinary retention and sepsis. After using prophylactic antibiotics, the incidence of septic complications is reduced to about 1%.

Color and Power Doppler Imaging

Doppler imaging is being used for detection of neovascularity associated with prostate cancer. This approach is especially useful to find isoechoic cancer because of the fact that pathology of these cancers show to have increased microvessel density. The hypoechoic sites that are vascular tend to have more tumor volume and higher Gleason score when evaluating biopsy. The power Doppler mode is more sensitive to detection of flow, gives a uniform display of vascular density, and gives images that are stable at different machine settings. There are some limitations with Doppler imaging. That is not all cancers are vascular. The absence of vascularity should not be taken as a point in deciding against the biopsy of a suspicious nodule and biopsy should be done in it.

Elastography

Prostate cancer areas are stiffer than areas with benign tissue. Areas containing cancer can be detected, but at present the overall detection is almost similar to systematic biopsy, and this procedure could not be used to avoid biopsy. Increased resistance has been found in chronic inflammation and atrophy also resulting in false postivity. Elastography would have a long learning curve wit high subjective nature and also those images are difficult to reproduce. New techniques using sound waves to produce tissue strainare developed to avoid variations seen with the technique of manual compression.

Contrast-Enhanced Ultrasonography and Targeted biopsy

The disadvantages of conventional B-Mode and colour Doppler ultrasound can be overcome by ultrasound contrast agents (UCA), which act as blood pool tracers and enable us to display the parenchymal microvasculature.

Ultrasound contrast agents remain in the intravascular space, but the most of the CT and MRI contrast agents are usually rapidly sent into the extracellular space, from the blood pool.

Multiple advantages of contrast ultrasound lies in its ability to assess dynamically about the contrast enhancement patterns in real time, as well as the possibility of performing repeated sonographic examinations.

The dynamic enhancement of the lesion is visualized either during intermittent or continuous scanning, but it depends on the contrast agent used and ultrasound mode.

ULTRASOUND CONTRAST AGENTS :(UCA)

First Generation UCA-Non Trans Pulmonary Vascular

Second Generation UCA-Trans Pulmonary, Vascular,Shory Half Life

Third Generation UCA-Trans Pulmonary, Vascular, Longer Half Life

UCAs have a micro bubble structure with gas bubbles which are stabilised by a shell. SonoVue is a second generation contrast agent with Phospholipid-stabilized microbubbles, with Sulfur hexafluoride gas.

UCA	SHELL	GAS	MANUFACTURER
Sonovue	Phospholipid	Sulphur hexafluride	Bracco
Levovist	Lipid	Air	Schering
Sonazoid	Lipid	Perfluorocarbon	Mallinckrodt/Nycomed-Amersham
Optison	Sonicated albumin	Octafluoropropane	Mallinckrodt/Nycomed-Amersham
Definity	Liposome	Perfluoropropane	Bristol Myers-Squibb

Dose:

One ml of sonovue has 8 µl of sulphur hexafluoride micro bubbles, equivalent to 45 micrograms. Dose required - B-mode imaging cardiac chambers, at rest or with stress requires 2 ml. For vascular Doppler imaging it is about 2.4 ml. In children < 18 years, the effectiveness and safety of this agent is not established and hence should not be used.

At clinical doses usually used, SonoVue produces marked increase in signal intensity for 3 to 8 minutes for microvasculature and macrovasculature Doppler imaging; and > 2 minutes for grey scale imaging.

Preparation and administration:

The contents of the vial are injected into 5 ml of sodium chloride 0.9%), for preparation of the contrast dispersion. The lyophilisate is dissolved completely, by shaking the vial vigorously for few seconds. For up to six hours after reconstitution , the dispersion of desired volume, can be drawn into a syringe.

SonoVue is injected into a peripheral vein, immediately, after it is drawn into the syringe . A 5 ml of sodium chloride (0.9%) flush is done after each injection.

Pharmacokinetic properties:

For the clinical dose, the amount of sulphur hexafloride gas injected is very small (16 µl of gas in a 2 ml dose). The gas, after dissolving in the blood, is exhaled through the lungs. The half-life of this agent was about 12 minutes. Within 2 minutes after injection, more than 80% of the gas administered, was exhaled and after 15 minutes, nearly 100% is exhaled.

Contraindications:

- History of hypersensitivity to UCA (sulphur hexafluoride).
- Evolving myocardial infarction,
- Acute cardiac failure,
- Recent coronary artery intervention,
- Pulmonary hypertension (severe),
- Severe rhythm disorders,
- Right-to-left shunts,
- Significant worsening of cardiac symptoms,
- Adult respiratory distress syndrome,
- Class III/IV cardiac failure,
- Angina at rest (within last 7 days),
- Pregnant and lactating women,
- Uncontrolled systemic hypertension.

Management:

Localized prostate cancer:

For clinically localized prostate cancer, standard treatment includes:

- Active surveillance
- Androgen deprivation therapy (ADT)
- Radical prostatectomy
- Radiation therapy

Metastatic prostate cancer:

Metastatic prostate cancer is not curable, and these cases are managed by:

- Therapy for relief of particular symptoms (eg, pain palliation)
- Measures to slow any further progression of the disease

Prognosis:

The Gleason grade, the margin positivity or capsular penetration (at the time of prostatectomy) and the tumor volume are the most important prognostic indicators for prostate cancer. High-grade prostatic carcinoma is often found with adverse pathologic findings and disease progression.

Seminal vesicle invasion and high-grade cancer are the main determinants of prostatic tumor–specific mortality.

The CAPRA (Cancer of the Prostate Risk Assessment) score for calculating prognosis is analyzed by:

- Age at diagnosis
- Gleason score
- PSA level
- Percentage positive biopsy cores
- Clinical tumor stage

This score is well accurate for predicting mortalities and metastases.

Molecular prognostic markers:

Several molecular markers were studied for determining the prognosis of patients, who are under treatment for localized as well as metastatic prostate cancers.

At present, none of them are measured in routine practice.

Morbidity and mortality:

It is the second most common etiology of cancer death in men, after lung carcinoma. Death rates have significantly decreased due to diagnosis of progressive disease at an earlier stage and also by improvements in the treatment of late stage disease.

Radical prostatectomy and radiation therapy leads to permanent side effects like urinary incontinence and erectile dysfunction.

Radiation therapy given for prostate cancer may lead to secondary malignancy, such as bladder cancer and rectal cancer.

MATERIALS AND METHODS

TITLE OF THE STUDY

Comparison of Contrast Enhanced Color Doppler Targeted Biopsy To Conventional Systematic Biopsy In Carcinoma Prostate.

TYPE OF STUDY

Prospective study

PERIOD OF STUDY

January 2013 – February 2014

PLACE OF STUDY

The study was conducted in Department of Urology and Radiology, Madras Medical College and Rajiv Gandhi Government Hospital , Chennai – 3

ETHICAL CLEARANCE

The institutional ethical review board at our hospital approved the study (No: 35032013)

INCLUSION CRITERIA

Patients with serum prostate specific antigen > 4 ng/ml

Normal or abnormal digital rectal examination

EXCLUSION CRITERIA

1. Active UTI
2. Prostatitis
3. Un Co-Operative Patients
4. Allergy to ultrasound contrast agents
5. Contra-indications to ultrasound contrast agents like -Recent acute myocardial infarction (< 7 days), Right-to-left shunts, Class III / IV cardiac failure, and severe pulmonary hypertension.

METHOD OF STUDY

Informed consent was obtained from all the patients. The patients were started on prophylactic antibiotic the night before biopsy. on the morning of biopsy, a cleansing enema was given for the patient. Aspirin or nonsteroidal anti-inflammatory agents are withheld for at least 5 days before biopsy.

Transrectal ultrasound examination of the prostate, TRUS examination during infusion of contrast material, and biopsy of the prostate are all done during a single visit. Transrectal sonography was performed with Siemens ultrasound machine for all patients. Contrast enhanced sonography was done using sonovue, as the ultrasound contrast agent. The lyophilized powder is shaken with 5 mL of distilled water for 20 sec. By using a 20-gauge cannula, 1.5 ml contrast agent bolus was

injected into the left antecubital vein manually. 1 ml solution contains 8ug/ml. 5 ml of normal saline is injected each time, after injecting the ultrasound contrast agent.

With a mechanical index of 0.6–1.2, contrast enhanced ultrasound was done, after contrast agent injection intravenously. 20 seconds of inter sweep delay were given, to prevent the unnecessary destruction of micro bubbles. From the prostatic base to the apex, contrast ultrasound was done. Each scan requires 5 to 10 sec depending upon the prostate volume. The entire imaging performed was repeated during infusion of contrast material. These images were obtained finally stored in digital format for further interpretation.

Targeted core biopsy is taken from contrast enhanced areas after administration of UCA. To avoid hyperemia produced by biopsy, contrast enhanced scanning is always done before systematic biopsy. Transitional zone is not biopsied

Fig 6 US Contrast Agent Sonovue

Subsequently, the same patient underwent systematic biopsy from 8 sites after imaging protocol. The prostate gland is divided into eight sites. They are apex; base; medial; and lateral portions of the mid gland, on the right and left sides. Biopsies were obtained using an 18 gauge biopsy needle. Ultrasound examination and biopsy takes about 30–40 minutes for each patient. Eight biopsy samples from each patient were sent in eight bottles separately, according to biopsy site for each patient. Biopsies were obtained without regard to prostate US appearance. In each biopsy specimen, the histopathological study was done to detect the presence of cancer foci and gleason grading was assigned to each core of biopsy.

The biopsies from contrast enhanced areas are sent separately and examined histopathologically for the presence of cancer foci and corresponding Gleason grading assigned.

In this study, 25 patients were biopsied. So, totally 25 x 8=200 sites were biopsied totally in these 25 patients. Also ,total biopsy cores from contrast enhanced sites from these 25 patients was 35.The number of patients were less but the number biopsy sites were very large , so this study is not limited by the number of samples.

Pathologic evaluation of the biopsy cores was the reference standard for calculation of sensitivity and specificity. The cancer detection rates of the 2 techniques and the Gleason scores between two techniques were compared.

Using Paired T test, specificity, sensitivity for prostate cancer detection was analyzed. Chi square test and ROC curve analysis were used.

In all the above statistical analysis, a *p* value of < 0.05 was considered significant.

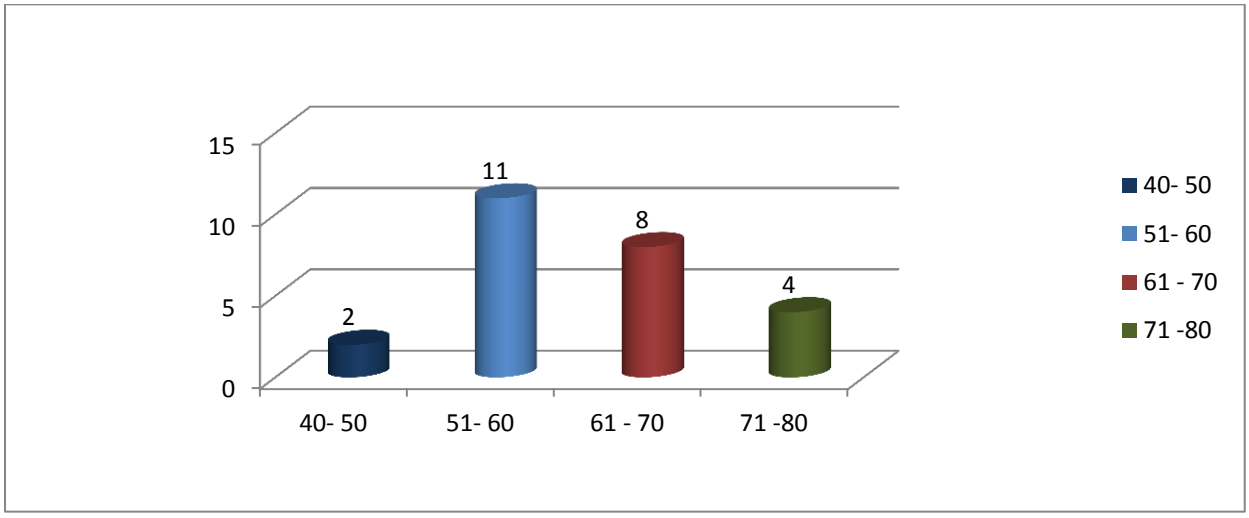
Ultrasound machine (Siemens Antares), Probe and Biopsy gun and Kit .

OBSERVATION AND RESULTS

Our study consists of 25 patients who are suspected to have carcinoma prostate either due to elevated serum PSA or abnormal digital rectal examination or both.

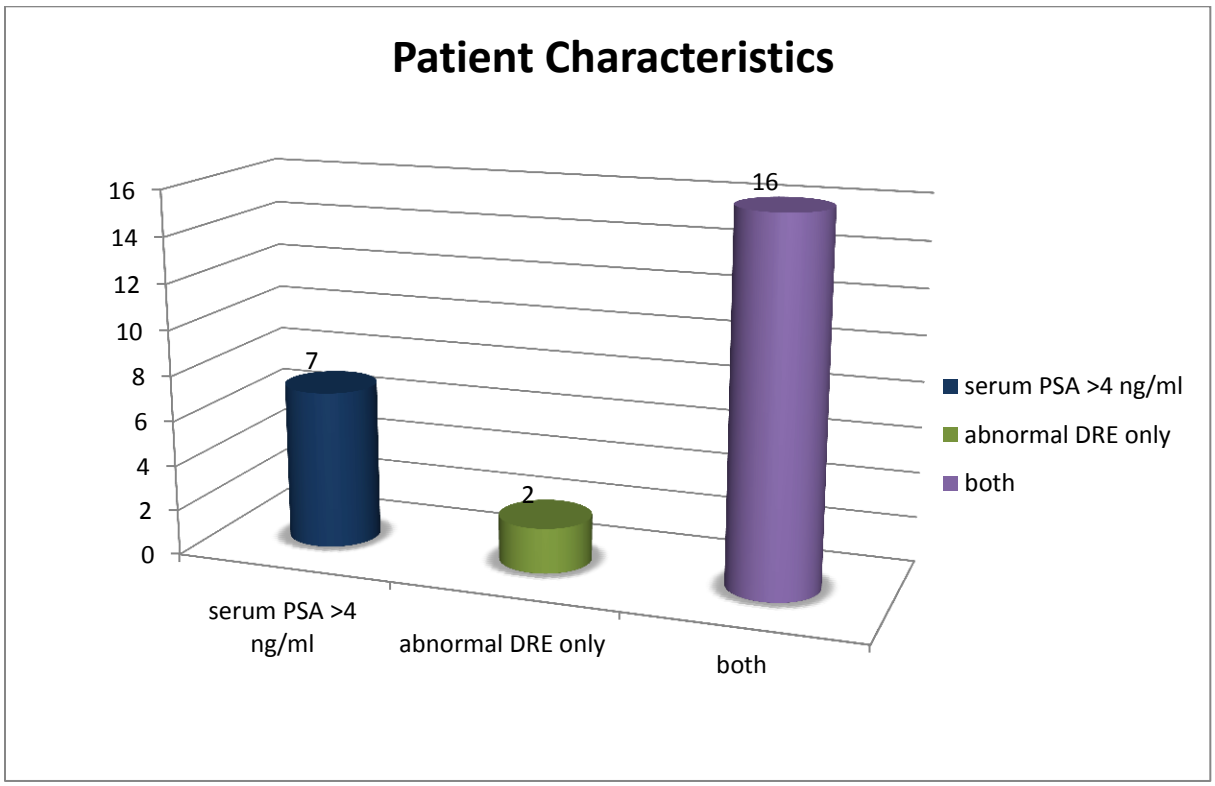
AGE DISTRIBUTION OF CASES

The subjects ranged in age from 41 – 80 years with a mean of 62.2 years.



PATIENT CHARACTERISTICS

Sixteen patients were included due to presence of both abnormal DRE and elevated serum.PSA>4 ng/ml. Two patients had only abnormal DRE with normal serum PSA. Seven patients had an elevated serum PSA alone with a normal DRE.

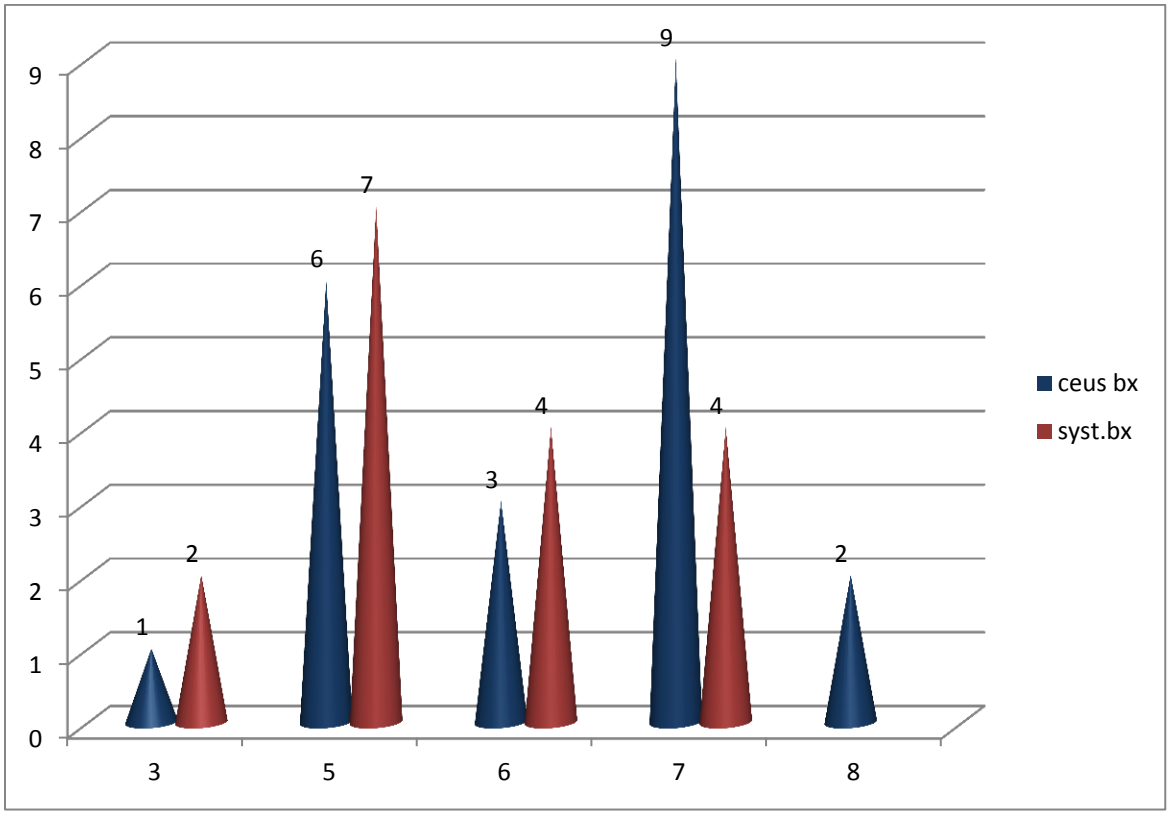


A total of 35 cores were taken from contrast enhanced areas out of which 26 cores were positive for malignancy. Out of 200 cores taken by systematic biopsy, 30 cores were positive. Separate Gleason score was given to each of the cores from contrast enhanced areas as well as systematic biopsy cores.

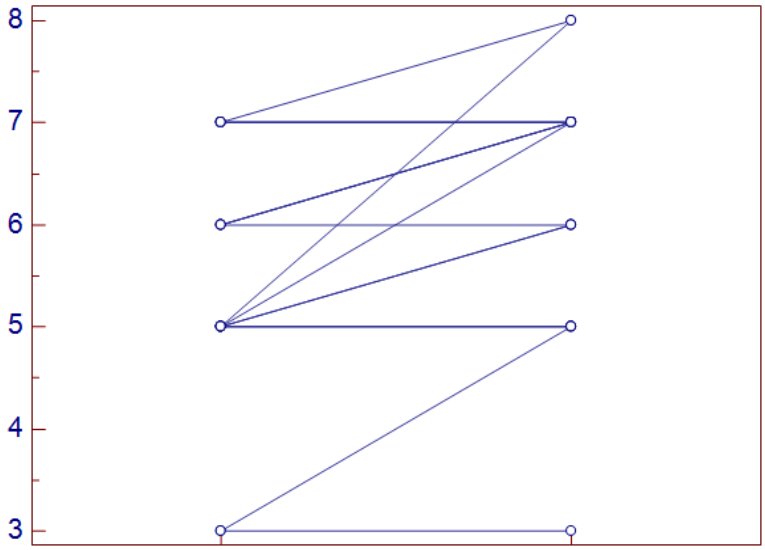
Gleason score distribution in contrast enhanced biopsy vs systematic biopsy

Biopsy from contrast enhanced areas showed a gleason score of 8 in 2 patients, seven in 9 patients, six in 3 patients, five in 6 patients and three in one patient. out of 25 cases,21 cases were positive for malignancy by contrast enhanced biopsy and 4 patients were negative for cancer. Out of this 4 patients,3 were BPH and 1 showed high grade PIN.

In the systematic biopsy group, a gleason score of 6 and 7 were present in 4 patients each, a score of 5 in 7 patients and 3 in 2 patient.



Higher grade cancer (Gleason score 7 or greater) was more common in patients with a positive targeted biopsy.



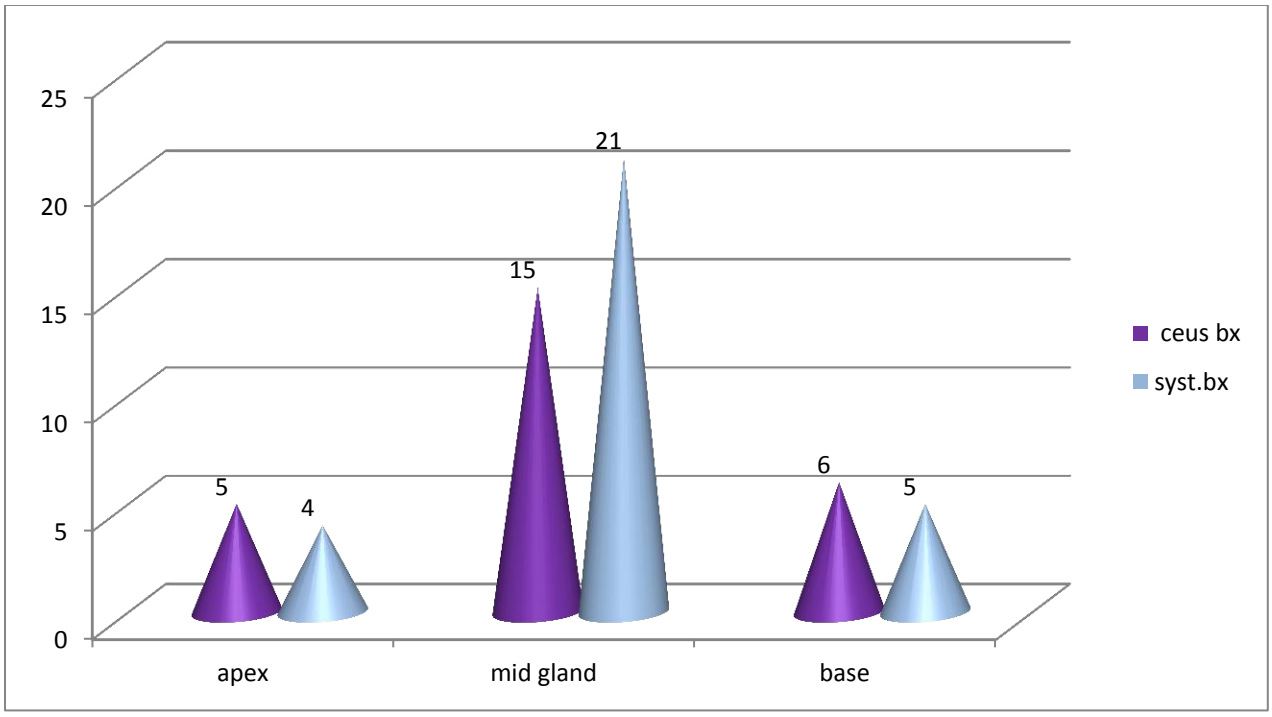
Dot-and-Line diagram

Systematic biopsy vs CEUS guided biopsy

Analysis by Paired samples t-test of gleason scores between systematic and contrast enhanced biopsy showed a 95% CI of 0.22 to 1.11 with a significant p value (p=0.0032).

Distribution of positive cores in contrast enhanced biopsy and systematic biopsy :

Prostate cancer were detected in the base (*n* = 6), mid gland (n=15), Apex (n=5) in contrast enhanced biopsy. In systematic biopsy, cancers were detected in base (n =5), mid gland (n =21),apex (n=4).

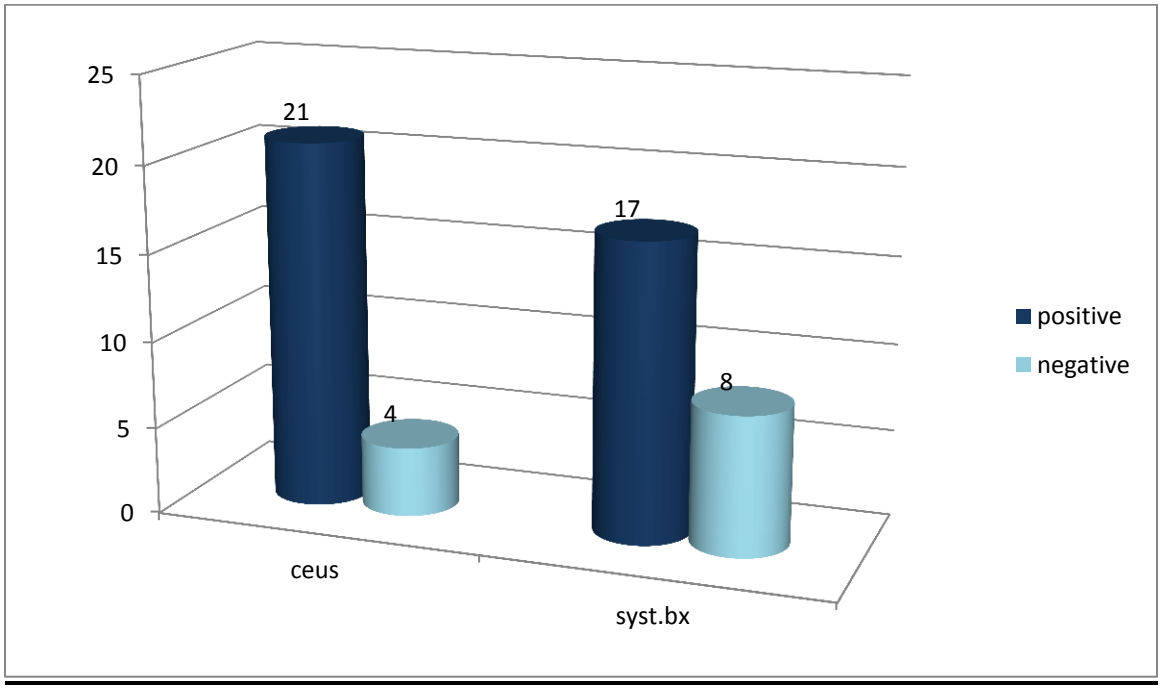


ULTRASONOGRAPHIC FINDINGS VS BIOPSY RESULTS

Findings at USG	Negative cores	Positive cores
Baseline TRUS		
NEGATIVE	**156**	**18**
POSITIVE	**14**	**12**
Contrast enhanced TRUS		
NEGATIVE	**5**	**-**
POSITIVE	**4**	**26**

Sensitivity and specificity for detection of prostate cancer was calculated using pathology of biopsy cores as reference standard. For baseline TRUS ,sensitivity was 40 % (12 /30) with specificity of 91.7%(156/170).For contrast enhanced ultrasound, sensitivity was 100 % (26/26) but specificity was 56%(5/9).Chi square and Exact Measures of Association showed a significant P value <0.0000001.

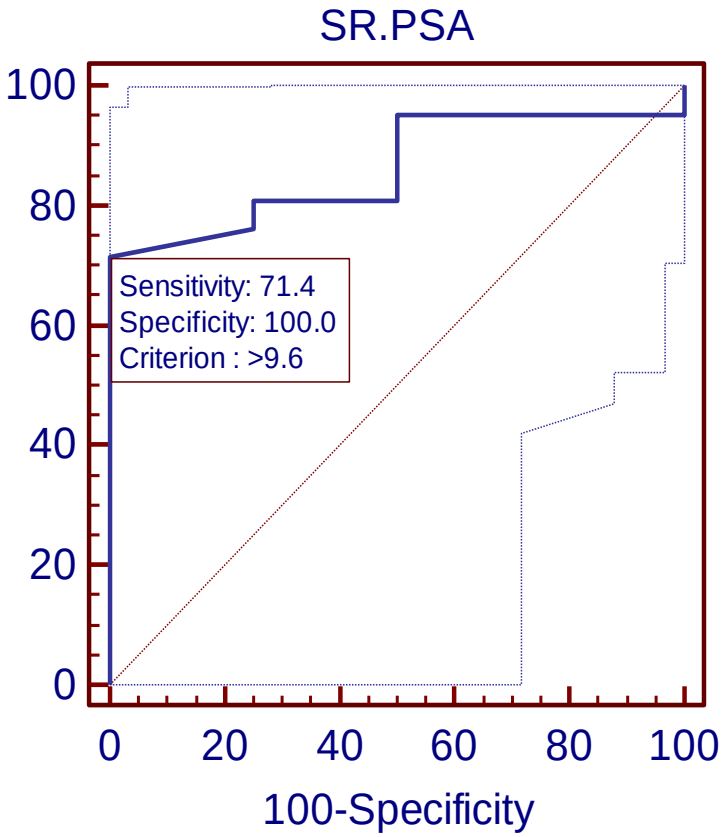
Standard TRUS and Contrast-Enhanced ultrasonography by Biopsy Site in 25 Patients:



Of the 25 patients evaluated, 21 patients showed positivity for prostate cancer by contrast enhanced TRUS biopsy. (84%).But systematic biopsy demonstrated cancer in 17 patients only out of the 25.(68%).

Sensitivity of contrast enhanced TRUS with respect to serum PSA:

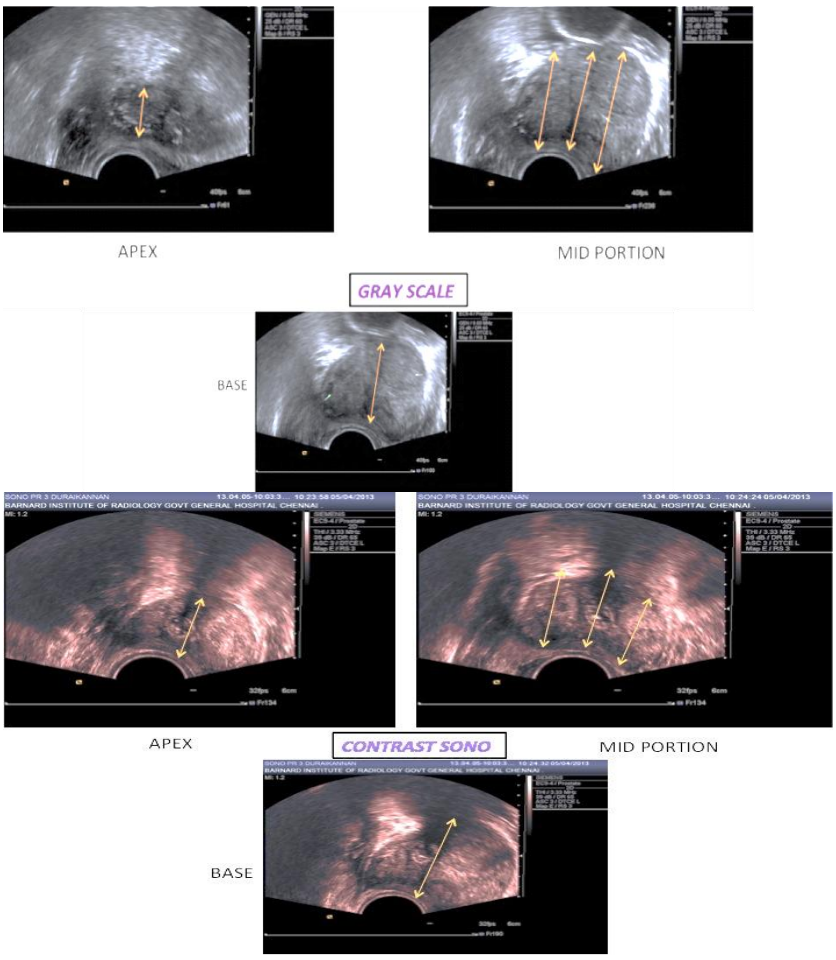
Our study included patients with serum PSA values ranging from 0.6 – 24.06 ng/ml with a mean of 12.73 .ROC analysis of sensitivity of contrast enhanced TRUS in relation to serum PSA showed area under curve of 0.863095 and 95% Confidence interval of 0.666917 to 0.966550 with a significant P value of <0.0001.



CASES

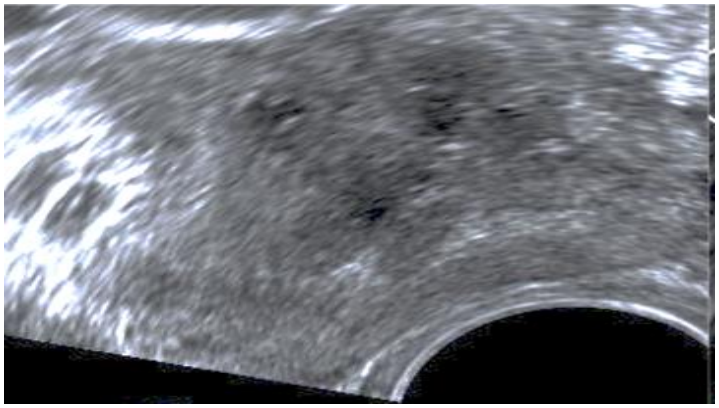
CASE 1:

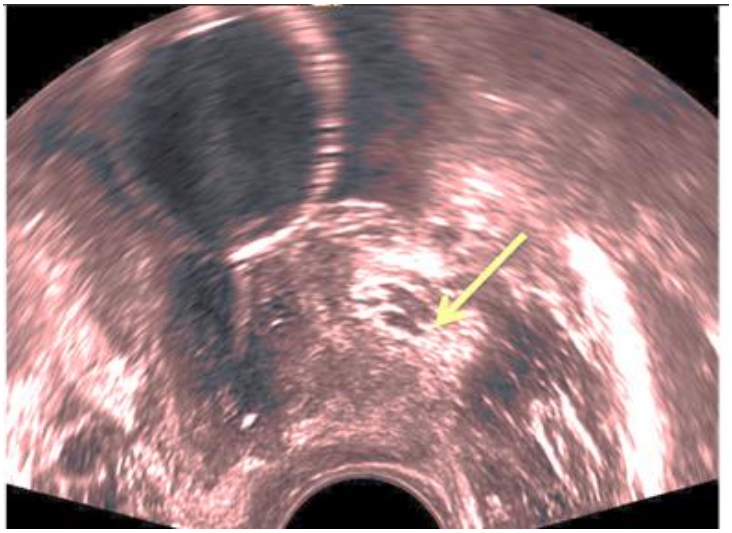
65 years male with urgency and hesitancy while passing urine past one year, with PSA level 9.1 ng/ml. Gray scale shows a nodule in left mid portion medially, laterally; left base and right base. Color Doppler shows increased vascularity in left mid portion medially, left apex. Contrast ultrasound shows increased enhancement in left base, apex, left mid portion medially, laterally, right base, right mid portion medially. HPE shows cancer in left base, apex, mid portion medial, lateral, right base.



Case 2:

62 years came with complaints of difficulty in passing urine and urgency past 6 months. His PSA level was 8.2 ng/ml. Lesion noted in the left base of the prostate, with focal enhancement on contrast ultrasound, was not seen in gray scale and color Doppler, which finally turned out to be cancer on HPE





DISCUSSION

For diagnosing prostate cancer, Transrectal ultrasonogram guided prostate systematic biopsy is the standard technique. Only a few studies were conducted in the past decade to analyze the efficacy of contrast enhanced ultrasound imaging for diagnosis of prostate carcinomas .Various studies gave different results, while analyzing the merit of contrast agent in prostate cancer. That too, most of the previous studies were done in patients with high prostate specific antigen(PSA),with only a few studies done in patients with indeterminate PSA levels , as the impact of diagnosing prostate cancer with ultrasound contrast agent will be much better appreciated if studies were done in those population.

Ethan J. Halpern, Ferdinand Frauscheret al study was,

"The value of the Ultrasound contrast targeted biopsy of the prostate gland cancer. Forty patients were examined with contrast agent, by using continuous intravenous infusion and following bolus of perfluteren microspheres. Cancer was detected in 30 biopsy samples in 16 of the patients.(40%).It was concluded that a suspicious site identified during contrast-enhanced sonography was 3.5 times more chance to have positive biopsy findings compared to an adjacent site that was not suspicious of cancer ($p < 0.025$). When a cancer suspected site was examined with an additional biopsy core, that site was diagnosed to have five times more likely to have a positive finding of cancer than the usual standard sextant site ($p < 0.01$).

They have found no significant difference in diagnostic accuracy between bolus and continuous infusion of contrast material."

Michael Mitterberge, WolfgangHorninger et al study[73] was, "A Randomized prospective trial comparing contrast-enhanced ultrasound targeted biopsy cores with gray-scale US guided systematic biopsy cores to determine their efficacy of the cancer detection rate. Cancer was found in 16 out of 50 subjects (32%) by targeted biopsy, and in 13 out of 50 patients (26%) with systematic biopsy. The cancer detection rate by targeted biopsy was significantly better than the systematic gray scale approach ($P < 0.04$, McNemar). The rate of cancer detection by using targeted biopsy cores (15.6% or 39/250 cores) was much significantly better than by using systematic core samples (6.8% or 34/500 cores, $P < 0.001$, McNemar). Contrast sonography targeted biopsy can detect more cancers than systematic biopsy with less number of biopsy cores."

In our study of 25 men, cancer was detected by CEUS and SB in 21(84%) and 17 (68%), respectively. The rate of detection of cancer by targeted biopsy was 74.2% or (26 of 35 cores) whereas the detection rate for systematic biopsy cores was 15% or(30 of 200). Cancer was missed in 4 patients (11.2%) which may be due to the fact that targeted biopsy were not taken from TZ cancers.

Operator dependence seems to be higher for the targeted technique than for the systematic one.

The appearance of microvessels in benign hyperplasia of prostate is very difficult to differentiate from those in cancer prostate. It might be possible that with new techniques, such as dynamic assessment of contrast agent enhancement, this problem will be overcome. However, this must be evaluated in further studies.

We performed 8 systematic and 1 core each from contrast enhanced area as targeted biopsies, which is completely different than a study design comparing 10 vs 15 cores. It has been demonstrated that multiple cores from single hypervascularized area were more likely to detect cancer than fewer less cores. Prostatitis may be associated with multiple hypervascularized areas .The main advantage of contrast enhanced TRUS is that it enhances areas of cancer which are not usually picked up by standard gray scale USG or those areas missed by systematic biopsy.

Our study demonstrates that contrast enhanced transrectal sonography, showed a statistically significant advantage for the detection of prostate cancer compared with conventional non-enhanced sonography. Contrast enhanced transrectal sonography is doubly sensitive than baseline sonogram for detection of prostate cancer with no substantial loss of specificity. There is a significant improvement in diagnostic accuracy with enhanced imaging, as shown by ROC analysis . It is clear from our study that contrast enhanced ultrasound picks up high grade lesions than regular TRUS biopsy.

The tumor grade, stage, volume, and microvascular density of carcinoma prostate are important from a clinical stand point. Persons with gleason score of two to four showed normal life expectancy when managed conservatively. Watchful waiting had a favourable prognosis in localized prostate cancer, according to a prospective study. So it is important to identify tumours in early stage to improve survival and treatment outcomes in patients with carcinoma prostate. Also unnecessary overtreatment should also be avoided.

Out of 25 patients, in our study, 21 were demonstrated to have cancer by both contrast enhancement and corresponding positive biopsy cores. The lesions shown in contrast enhanced cores were of higher gleason grade when compared to systematic biopsy.

We took a total of 200 biopsy cores from 25 patients by conventional TRUS examination. Out of these 200 cores, only 30 cores were positive for malignancy indicating the need for more number of cores for detecting lesser cancers. Biopsy from target lesions helps in identifying more cancers of higher grade in lesser cores, thereby decreasing complications of biopsy.

The identification of higher grade cancers in targeted biopsy in the same patients who have a lower grade due to regular biopsy has a significant impact on treatment.

Conclusion

The results of this study shows that

The sensitivity and accuracy of cancer detection is improved by using ultrasound contrast agents for depicting microvessels in carcinoma prostate.

The use contrast agents in TRUS will help in targeted biopsy of the enhancing lesions thereby decreasing the number of biopsy cores and associated complication.

The use of CEUS also may be useful in patients with indeterminate serum PSA.

Targeted biopsy has a definite impact on gleason scores, detecting high grade cancers with limited number of cores thus helping in planning the treatment in carcinoma prostate.

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APPENDIX I

INFORMED CONSENT FORM

Title of the study:

"COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE"

Name of the Participant:

Name of the Principal (Co-Investigator):

DR.J.INDUJA

Name of the Institution: Rajiv Gandhi Govt General Hospital, Chennai – 3

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "**COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE"**

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have been informed the investigator of all the treatments I am taking or have taken in the past 3 months including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

8. I have not participated in any research study within the past 6 month(s)

10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____

Date_____

For Children being enrolled in research:

Whether child's assent was asked: Yes / No (Tick one)

[If the answer to be above question is yes, write the following phrase:

You agree with the manner in which assent was asked for from your child and given by your child. You agree to have your child take part in this study].

[If answer to be above question No, give reason (s) :_____.

Although your child did not or could not give his or her assent, you agree to your child's Participation in this study.

Name and Signature of / thumb impression of the participant's parent(s) (or legal representative)

Name _____ Signature_____

Date_____

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for parents of participant child illiterate):

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness: _____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____

Date_____

ஆராய்ச்சி ஒப்புதல் கடிதம்

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்று நோயைக் கண்டறிய வண்ண உள்ளுருப்படம் மூலம் சதைப் பிரிசோதனை எடுத்தல் முறைக்கும் முறையான சதைப்பரிசோதனை முறைக்கும் இடையான ஒப்பீட்டாய்வு

பெயர் : தேதி :
வயது : உள்/புற நோயாளி எண். :
பால் : ஆராய்ச்சி சேர்க்கை எண். :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

ஏனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்று நோயைக் கண்டறிய வண்ண உள்ளுருப்படம் மூலம் சதைப் பிரிசோதனை எடுத்தல் முறைக்கும் முறையான சதைப்பரிசோதனை முறைக்கும் இடையான ஒப்பீட்டாய்வு ஆராய்ச்சிக்கு தேவையான அனைத்து விவரங்களையும் தெரியப்படுத்துவதற்கு நான் முழுசம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்று நோயைக் கண்டறிய வண்ண உள்ளுருப்படம் மூலம் சதைப் பிரிசோதனை எடுத்தல் முறைக்கும் முறையான சபைப்பரிசோதனை முறைக்கும் இடையான ஒப்பீட்டாய்வு ஆராய்ச்சி பற்றிய தகவல் தாளை நான் பெற்றுக் கொண்டேன்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும, சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்து கொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதம்.

நோயாளியின் பெயர் கையொப்பம்/இடது பெருவிரல் ரேகை தேதி

ஆராய்ச்சியாளரின் பெயர் கையொப்பம் தேதி

Appendix II

PROFORMA

Title

"COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE**"**

Sl.No: Date:

Name: IP No:

Age/Sex:

Occupation:

Address:

Presenting Complaints

Duration :

Others :

Past History

Vital signs

Pulse :

BP :

Respiratory rate :

General Examination

Built :

Anemia :

Per rectal Examination

Lab finding-

Urine routine

Urine culture and sensitivity

BT/CT

Complete blood count

Renal function test

Serum PSA level (ng/ml)-

Transrectal ultrasound:

Prostate region	***Gray scale***	***Ultrasound contrast (enhancement)***
Right base		
Left base		
Right medial mid portion		
Right lateral mid portion		
Left medial mid portion		
Left lateral mid portion		
Right apex		
Left apex		

HPE report

Number of cores positive - conventional TRUS / contrast enhanced TRUS

Gleason grade of each positive core

NAME	AGE	SR. PSA	DRE	cont.enhancement	NO.OF POS. CORES	GLEASON GRADE	SYSTEMATIC BIOPSY								NO.OF. POS. CORES	gleason score
							rt. base	**lt. base**	**rt.mid - med**	**rt.mid-lat**	**lt.mid-med**	**lt.mid-lat**	**rt. apex**	**lt. apex**		
paulraj	65/m	21.9	NODULAR	RT.LAT/LT.LAT	2	5+3	neg	neg	pos	pos	neg	pos	neg	neg	3	3+2
govindan	78/m	16.7	NODULAR	RT.MID GL	1	4+3	neg	neg	neg	pos	neg	neg	neg	neg	1	3+3
duraikannan	70/m	13	NORMAL	RT.MID GL/LT.MID.GL	2	3+2	neg	neg	pos	neg	neg	pos	neg	neg	2	3+2
vellai	65/m	15	NODULAR	Lt.apex,mid gl	1	3+3	neg	neg	neg	neg	pos	pos	neg	neg	2	3+2
bahavandas	46/m	9.6	NORMAL	lt.base	1	3+2	neg	neg	neg	neg	neg	neg	neg	neg	0	0
rathinavelu	60/m	4.6	NODULAR	rt.mid gl	1	4+3	neg	neg	pos	neg	neg	neg	neg	neg	1	4+3
subramani	60/m	17.6	NORMAL	lt.apex	1	4+2	neg	neg	neg	neg	neg	neg	neg	pos	0	3+2
santhanam	60/m	0.9	NODULAR	neg	0	0	neg	neg	neg	neg	neg	neg	neg	neg	0	0
krishnan	60/m	23.3	NODULAR	lt.base/lt.mid	1	3+4	neg	pos	pos	neg	pos	pos	neg	neg	4	3+3
Ibrahim sheriff	70/m	16	NODULAR	lt.mid gl	1	3+4	neg	neg	neg	neg	neg	neg	neg	neg	0	0
Dheenadhayalan	60/m	6.2	NORMAL	rt.apex	1	5+3	neg	neg	pos	neg	neg	neg	pos	neg	2	3+4

kumar	52/m	0.6	NODULAR	RT.MID GL/LT.MID.GL	1	2+1	neg	neg	neg	neg	pos	neg	neg	neg	1	2+1
boopalan	55/m	18.2	NODULAR	lt.base	1	3+2	neg	pos	neg	neg	neg	neg	neg	neg	1	3+2
dakshinamoorthi	60/m	24.1	NODULAR	lt.mid/lt.base	2	3+4	neg	pos	neg	neg	pos	pos	neg	neg	3	3+4
arjunan	55/m	6.7	NORMAL	rt.apex	0	BPH	neg	neg	neg	neg	neg	neg	neg	neg	0	0
kailasam	69/m	4.2	NODULAR	lt.mid/lt.base	0	PIN	neg	neg	neg	neg	neg	neg	neg	neg	0	0
natarajan	72/m	24.8	NODULAR	lt.mid/apex/base	3	4+3	neg	pos	neg	neg	pos	neg	neg	pos	3	3+3
dhamodharan	60/m	17.6	NODULAR	rt.apex	1	4+3	neg	neg	neg	pos	neg	neg	pos	neg	2	4+3
munusamy	70/m	9.29	NORMAL	lt.mid	1	2+1	neg	neg	neg	neg	neg	neg	neg	neg	0	0
dhayalan	53/m	5.47	NODULAR	rt.med	1	3+2	neg	neg	neg	pos	neg	neg	neg	neg	1	2+1
vaiyapuri	76/m	12.8	NODULAR	rt.base/mid gl	1	4+3	neg	neg	pos	neg	neg	neg	neg	neg	1	3+2
arumugam	63/m	13.3	NODULAR	lt.apex	1	3+3	neg	neg	neg	neg	neg	pos	neg	neg	1	3+3
abdul lateef	62/m	23.1	NODULAR	lt.mid gl	1	4+3	neg	neg	neg	neg	pos	neg	neg	neg	1	4+3
krishnamoorthi	75/m	9.6	NORMAL	rt.mid	0	0	neg	neg	neg	neg	neg	neg	neg	neg	0	0
thangaraj	41/m	16	NODULAR	lt.mid/rt.base	1	3+2	pos	neg	neg	neg	neg	neg	neg	neg	1	3+2
				35	26										30	

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.J.Induja,
II year M.ch Urology,
MMC,Chennai – 3.

Dear J.INDUJA

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Comparision of contrast Enhanced color Doppler Targeted Biopsy to conventional systematic Biopsy in carcinoma prostate " No.35032013.

The following members of Ethics Committee were present in the meeting held on 05.03.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. A. Radhakrishnan MD -- Member
   Prof of Internal Medicine, MMC, Ch-3
6. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nandhini
Member Secretary, Ethics Committee

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INTRODUCTION

One of the the most common cancer diagnosed in men is carcinoma prostate.Because of improvements in diagnostic testing,its incidence has been increasing.In patients with carcinoma prostate, ultrasonogram guided biopsy has been the investigation of choice in men with increased serum prostate specific antigen or a nodular prostate.Targeted biopsies will be helpful in increasing the sensitivity of systematic biopsy.

Micro-bubble contrast agents are used as innovative technology to enhance detection of prostatic cancer.Several studies have demonstrated that contrast enhanced ultrasound (CEUS) of prostatic blood flow helps in visualization of cancerous lesion and to target biopsy.Biopsy from target lesion helps in detecting more cancers with lesser cores .CEUS has been shown to detect cancers with higher Gleason scores,which improves cancer grading.

Microbubble contrast agent images the microvasculature in the prostate,especially in carcinoma.Such contrast agents increase the sensitivity in detecting carcinomatous lesions.

We undertook this study to find the efficacy of CC sonography for detection of prostate in patients with PSA >4 ng/ml and compare this with conventional systems.

thesis

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APPENDIX I

INFORMED CONSENT FORM

Title of the study:

"COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE"

Name of the Participant:

Name of the Principal (Co-Investigator):

DR.J.INDUJA

Name of the Institution: Rajiv Gandhi Govt General Hospital, Chennai – 3

Documentation of the informed consent

I _____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in "**COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE"**

1. I have read and understood this consent form and the information provided to me.

2. I have had the consent document explained to me.

3. I have been explained about the nature of the study.

4. I have been explained about my rights and responsibilities by the investigator.

5. I have been informed the investigator of all the treatments I am taking or have taken in the past 3 months including any native (alternative) treatment.

6. I have been advised about the risks associated with my participation in this study.

7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms.

8. I have not participated in any research study within the past 6 month(s)

10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital.

11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent.

12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.

13. I have understand that my identity will be kept confidential if my data are publicly presented

14. I have had my questions answered to my satisfaction.

15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document.

For adult participants:

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for illiterate patients):

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____

Date_____

For Children being enrolled in research:

Whether child's assent was asked: Yes / No (Tick one)

[If the answer to be above question is yes, write the following phrase:

You agree with the manner in which assent was asked for from your child and given by your child. You agree to have your child take part in this study].

[If answer to be above question No, give reason (s) :_____.

Although your child did not or could not give his or her assent, you agree to your child's Participation in this study.

Name and Signature of / thumb impression of the participant's parent(s) (or legal representative)

Name _____ Signature_____

Date_____

Name _____ Signature_____

Date_____

Name and Signature of impartial witness (required for parents of participant child illiterate):

Name _____ Signature_____

Date_____

Address and contact number of the impartial witness: _____

Name and Signature of the investigator or his representative obtaining consent:

Name _____ Signature_____

Date_____

ஆராய்ச்சி ஒப்புதல் கடிதம்

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்று நோயைக் கண்டறிய வண்ண உள்ளுருப்படம் மூலம் சதைப் பிரிசோதனை எடுத்தல் முறைக்கும் முறையான சதைப்பரிசோதனை முறைக்கும் இடையான ஒப்பீட்டாய்வு

பெயர் : தேதி :
வயது : உள்/புற நோயாளி எண். :
பால் : ஆராய்ச்சி சேர்க்கை எண். :

இந்த ஆராய்ச்சியின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

ஏனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்று நோயைக் கண்டறிய வண்ண உள்ளுருப்படம் மூலம் சதைப் பிரிசோதனை எடுத்தல் முறைக்கும் முறையான சதைப்பரிசோதனை முறைக்கும் இடையான ஒப்பீட்டாய்வு ஆராய்ச்சிக்கு தேவையான அனைத்து விவரங்களையும் தெரியப்படுத்துவதற்கு நான் முழுசம்மதம் தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்து கொண்டேன்.

சுக்கிய (ப்ராஸ்டேட்) சுரப்பி புற்று நோயைக் கண்டறிய வண்ண உள்ளுருப்படம் மூலம் சதைப் பிரிசோதனை எடுத்தல் முறைக்கும் முறையான சபைப்பரிசோதனை முறைக்கும் இடையான ஒப்பீட்டாய்வு ஆராய்ச்சி பற்றிய தகவல் தாளை நான் பெற்றுக் கொண்டேன்.

இந்த ஆராய்ச்சியினால் ஏற்படும் நன்மைகளையும, சில பக்கவிளைவுகளையும் பற்றி தெளிவாக மருத்துவர் மூலம் தெரிந்து கொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக் கொள்ள சம்மதம்.

நோயாளியின் பெயர் கையொப்பம்/இடது பெருவிரல் ரேகை தேதி

ஆராய்ச்சியாளரின் பெயர் கையொப்பம் தேதி

Appendix II

PROFORMA

Title

"COMPARISON OF CONTRAST ENHANCED COLOR DOPPLER TARGETED BIOPSY TO CONVENTIONAL SYSTEMATIC BIOPSY IN CARCINOMA PROSTATE**"**

Sl.No: Date:

Name: IP No:

Age/Sex:

Occupation:

Address:

Presenting Complaints

Duration :

Others :

Past History

Vital signs

Pulse :

BP :

Respiratory rate :

General Examination

Built :

Anemia :

Per rectal Examination

Lab finding-

Urine routine

Urine culture and sensitivity

BT/CT

Complete blood count

Renal function test

Serum PSA level (ng/ml)-

Transrectal ultrasound:

Prostate region	***Gray scale***	***Ultrasound contrast (enhancement)***
Right base		
Left base		
Right medial mid portion		
Right lateral mid portion		
Left medial mid portion		
Left lateral mid portion		
Right apex		
Left apex		

HPE report

Number of cores positive - conventional TRUS / contrast enhanced TRUS

Gleason grade of each positive core

NAME	AGE	SR. PSA	DRE	cont.enhancement	NO.OF POS. CORES	GLEASON GRADE	SYSTEMATIC BIOPSY								NO.OF. POS. CORES	gleason score
							rt. base	**lt. base**	**rt.mid - med**	**rt.mid-lat**	**lt.mid-med**	**lt.mid-lat**	**rt. apex**	**lt. apex**		
paulraj	65/m	21.9	NODULAR	RT.LAT/LT.LAT	2	5+3	neg	neg	pos	pos	neg	pos	neg	neg	3	3+2
govindan	78/m	16.7	NODULAR	RT.MID GL	1	4+3	neg	neg	neg	pos	neg	neg	neg	neg	1	3+3
duraikannan	70/m	13	NORMAL	RT.MID GL/LT.MID.GL	2	3+2	neg	neg	pos	neg	neg	pos	neg	neg	2	3+2
vellai	65/m	15	NODULAR	Lt.apex,mid gl	1	3+3	neg	neg	neg	neg	pos	pos	neg	neg	2	3+2
bahavandas	46/m	9.6	NORMAL	lt.base	1	3+2	neg	neg	neg	neg	neg	neg	neg	neg	0	0
rathinavelu	60/m	4.6	NODULAR	rt.mid gl	1	4+3	neg	neg	pos	neg	neg	neg	neg	neg	1	4+3
subramani	60/m	17.6	NORMAL	lt.apex	1	4+2	neg	neg	neg	neg	neg	neg	neg	pos	0	3+2
santhanam	60/m	0.9	NODULAR	neg	0	0	neg	neg	neg	neg	neg	neg	neg	neg	0	0
krishnan	60/m	23.3	NODULAR	lt.base/lt.mid	1	3+4	neg	pos	pos	neg	pos	pos	neg	neg	4	3+3
Ibrahim sheriff	70/m	16	NODULAR	lt.mid gl	1	3+4	neg	neg	neg	neg	neg	neg	neg	neg	0	0
Dheenadhayalan	60/m	6.2	NORMAL	rt.apex	1	5+3	neg	neg	pos	neg	neg	neg	pos	neg	2	3+4

kumar	52/m	0.6	NODULAR	RT.MID GL/LT.MID.GL	1	2+1	neg	neg	neg	neg	pos	neg	neg	neg	1	2+1
boopalan	55/m	18.2	NODULAR	lt.base	1	3+2	neg	pos	neg	neg	neg	neg	neg	neg	1	3+2
dakshinamoorthi	60/m	24.1	NODULAR	lt.mid/lt.base	2	3+4	neg	pos	neg	neg	pos	pos	neg	neg	3	3+4
arjunan	55/m	6.7	NORMAL	rt.apex	0	BPH	neg	neg	neg	neg	neg	neg	neg	neg	0	0
kailasam	69/m	4.2	NODULAR	lt.mid/lt.base	0	PIN	neg	neg	neg	neg	neg	neg	neg	neg	0	0
natarajan	72/m	24.8	NODULAR	lt.mid/apex/base	3	4+3	neg	pos	neg	neg	pos	neg	neg	pos	3	3+3
dhamodharan	60/m	17.6	NODULAR	rt.apex	1	4+3	neg	neg	neg	pos	neg	neg	pos	neg	2	4+3
munusamy	70/m	9.29	NORMAL	lt.mid	1	2+1	neg	neg	neg	neg	neg	neg	neg	neg	0	0
dhayalan	53/m	5.47	NODULAR	rt.med	1	3+2	neg	neg	neg	pos	neg	neg	neg	neg	1	2+1
vaiyapuri	76/m	12.8	NODULAR	rt.base/mid gl	1	4+3	neg	neg	pos	neg	neg	neg	neg	neg	1	3+2
arumugam	63/m	13.3	NODULAR	lt.apex	1	3+3	neg	neg	neg	neg	neg	pos	neg	neg	1	3+3
abdul lateef	62/m	23.1	NODULAR	lt.mid gl	1	4+3	neg	neg	neg	neg	pos	neg	neg	neg	1	4+3
krishnamoorthi	75/m	9.6	NORMAL	rt.mid	0	0	neg	neg	neg	neg	neg	neg	neg	neg	0	0
thangaraj	41/m	16	NODULAR	lt.mid/rt.base	1	3+2	pos	neg	neg	neg	neg	neg	neg	neg	1	3+2
				35	26										30	

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3
Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.J.Induja,
II year M.ch Urology,
MMC,Chennai – 3.

Dear J.INDUJA

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Comparision of contrast Enhanced color Doppler Targeted Biopsy to conventional systematic Biopsy in carcinoma prostate " No.35032013.

The following members of Ethics Committee were present in the meeting held on 05.03.2013 conducted at Madras Medical College, Chennai -3.

1. Dr.SivaKumar, MS FICS FAIS --- Chairperson
2. Prof. R. Nandhini MD -- Member Secretary
   Director, Instt. of Pharmacology ,MMC, Ch-3
3. Prof. Shyamraj MD -- Member
   Director i/c , Instt. of Biochemistry , MMC, Ch-3
4. Prof. P. Karkuzhali. MD -- Member
   Prof., Instt. of Pathology, MMC, Ch-3
5. Prof. A. Radhakrishnan MD -- Member
   Prof of Internal Medicine, MMC, Ch-3
6. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
7. Thiru. S. Govindsamy. BABL -- Lawyer
8. Tmt. Arnold Saulina MA MSW -- Social Scientist

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

R Nandhini
Member Secretary, Ethics Committee

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INTRODUCTION

One of the the most common cancer diagnosed in men is carcinoma prostate.Because of improvements in diagnostic testing,its incidence has been increasing.In patients with carcinoma prostate, ultrasonogram guided biopsy has been the investigation of choice in men with increased serum prostate specific antigen or a nodular prostate.Targeted biopsies will be helpful in increasing the sensitivity of systematic biopsy.

Micro-bubble contrast agents are used as innovative technology to enhance detection of prostatic cancer.Several studies have demonstrated that contrast enhanced ultrasound (CEUS) of prostatic blood flow helps to visualization of cancerous lesion and to target biopsy.Biopsy from target lesion helps in detecting more cancers with lesser cores .CEUS has been shown to detect cancers with higher Gleason scores,which improves cancer grading.

Microbubble contrast agent images the microvasculature in the prostate,especially in carcinoma.Such contrast agents increase the sensitivity in detecting carcinomatous lesions.

We undertook this study to find the efficacy of CC sonography for detection of prostate in patients with PSA >4 ng/ml and compare this with conventional systems.

thesis

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